HEMOGLOBIN PLASMA PROTEIN and CELL PROTEIN

G. H. Whipple, M.D.

2704

1. hemoglobin plasma proteins
2. hemoglobin (3) globin
4. nitrogen balances. (5) anemia
6. hypoproteinemia (7) amino acids
8. methionine (9) liver injury
10. body proteins
11. hemoglobin production
12. infection lessens blood proteins
13. liver (14) metebolism
15. eck fistula liver (16) stimuli

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HEMOGLOBIN
PLASMA PROTEIN
AND
CELL PROTEIN

Their Production and Interchange

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Their Production and Interchange

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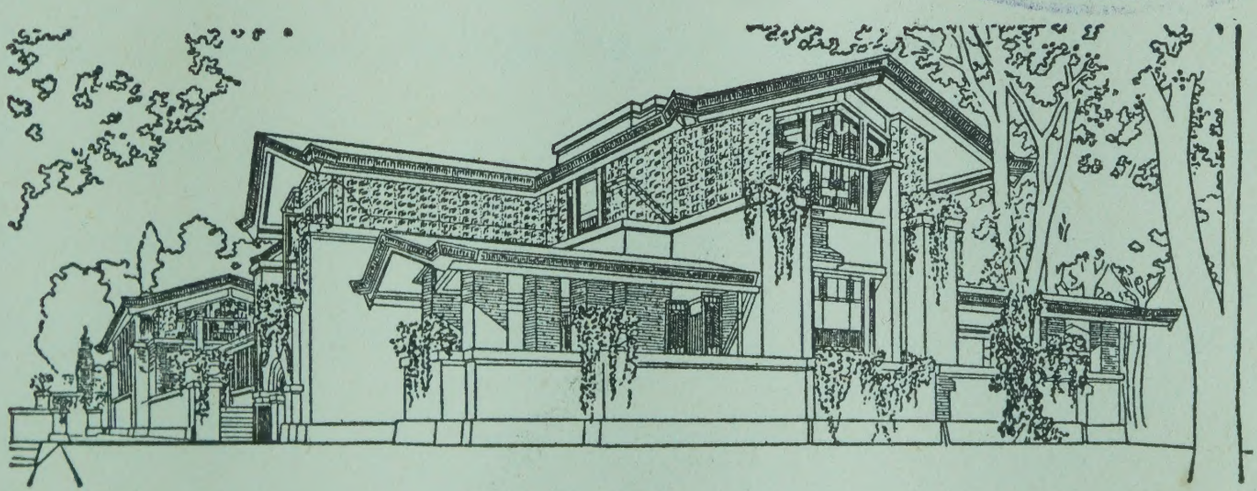

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HEMOGLOBIN
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AND
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Their Production and Interchange

Introduction

This lecture at the request of the editor, is not designed to supply a review of this great field—rather an exposition of our concepts of blood protein metabolism, with illustrative tables taken from the work of this laboratory. We assume that the food proteins yield the amino acids absorbed from the intestinal tract and that these amino acids are synthesized in the liver (and elsewhere) into plasma proteins. The plasma proteins (and amino acids) supply the protein requirements of the body cells. Normally

TABLE 1

Hemoglobin and Plasma Protein in Body Circulation and in Reserve Stores
Regenerative Capacity of Dog

	Circulating mass	Maximal regenerative capacity per week	Reserve store
	gm.	*gm.*	*gm.*
Hemoglobin	180	50–70	50–200
Plasma protein	30	50–70+	30–100

Dog ten kilos = 900 cc. blood volume = 500 cc. plasma volume.
Twenty gm. and six gm. per cent = normal hemoglobin and plasma protein.

(From Whipple, G. H., and Madden, S. C.: *Medicine, 23:* 217, 1944.)

there is a considerable *reserve* of hemoglobin and plasma protein forming material (Table 1) and this reserve may be reduced by fasting, low protein diet, bleeding or plasma depletion. This depletion of protein reserves lowers the body resistance to infection (10) and intoxication (12). The question of protein depletion and lowered resistance to infection is to be treated in detail in another lecture in this series (22).

Protein Dynamic Equilibrium

These body protein stores, protein production, protein wear and tear, or protein loss are in a nicely balanced or *steady state*—a dynamic equilibrium. These proteins can pass readily from plasma

into cells or from cells into plasma without loss of nitrogen. Whatever our concept of protein molecules and their passage through cell surfaces, we are forced to the conclusion that protein does pass through cell surfaces readily as a part of normal protein metabolic exchange. The term "protein pool" suggests that within the total

TABLE 2

Intraperitoneal Hemoglobin Contributes to Plasma Protein and Hemoglobin Production in Anemia and Hypoproteinemia

Period 1 wk.	Weight	Protein intake		Protein output				Production ratio plasma protein to hemoglobin	Total nitrogen	
		Type	Weekly	Hemoglobin		Plasma protein			Intake	Urinary output
				Level	Output per wk.	Level	Output per wk.			
	kg.		*gm.*	*gm. per cent*	*gm.*	*gm. per cent*	*gm.*	*per cent*	*gm.*	*gm.*
Dog 37-23 Dog hemoglobin—intraperitoneal										
1	21.9	Basal	22	8.0	62.0	4.9	32.2	52	3.5	11.9
2	20.9	Basal	20	6.7	19.5	4.7	11.0	56	3.2	10.9
3	19.4	Hb—31.9 gm.	30.7	9.4	57.3	5.4	25.8	45	5.2	8.2
4	19.2	Hb—42.9 gm.	40.8	8.1	48.2	4.8	21.7	45	6.9	8.3
5	18.9	Hb—44.0 gm.	42.2	9.4	12.9	4.5	5.8	45	7.1	8.7
6	17.9	Basal	15	8.2	25.5	4.3	11.1	44	2.4	6.2
7	17.0	Basal	11	8.2	1.6	4.4	0	—	1.8	6.3
Dog 37-82 Dog hemoglobin—intraperitoneal										
1	17.1	Basal	18	7.7	16.2	4.6	9.5	59	2.8	8.4
2	16.4	Hb—38.6 gm.	37	10.9	12.9	4.5	5.8	45	6.2	7.1
3	15.9	Hb—60.7 gm.	58	10.7	45.5	4.7	19.7	43	9.3	6.8
4	15.3	Hb—44.2 gm.	51	11.7	18.3	4.3	7.3	40	8.6	6.4
5	14.7	Basal	9	11.7	1.7	3.4	0	—	1.4	5.3

(From Miller, L. L., Robscheit-Robbins, F. S., and Whipple, G. H.: *J. Exp. Med., 81:* 416, 1945.)

mass of body protein there is a fluid interchange between the proteins in cells, in reserve stores, in production, in utilization and circulation.

Hemoglobin in its production may derive in part from plasma protein, but hemoglobin contributes to the "protein pool" for exchange only when the red cell wears out or is destroyed and then after separation of the iron and complete loss of the pigment radical to the liver and bile (Table 4).

Table 2 (dog 37-82) shows a very convincing experiment in which the urinary nitrogen balance is positive and the nitrogen conservation maximal. Dog 37-23 shows a negative balance. A total of 144 gm. hemoglobin was given intraperitoneally and a net production of 107 gm. hemoglobin plus thirty gm. plasma protein removed. All evidence indicates complete utilization of the introduced globin (hemoglobin) to make new hemoglobin and new plasma protein and to participate in the internal protein metabolism. There is considerable weight loss, which presumably means a contribution from the body proteins to the circulating proteins and to normal nitrogen wastage in the urine.

Hemoglobin, Globin and Nitrogen Balance

Globin from hemoglobin is broken down in the body continuously due to red cell obsolescence and is obviously perfectly suited to build new hemoglobin with the addition of iron and the pigment radicle. These experiments (11) show that globin contributes to the "protein pool" material which serves well the protein requirements of the body. *Nitrogen balance* can be attained in dogs with *normal blood* when abundant laked red cells are given intraperitoneally and a basal ration supplies the needed carbohydrates, fats, minerals, and vitamin accessories. Globin is not as effectively used as is plasma protein and there is a larger nitrogen output in the globin experiments but these dogs remain close to nitrogen and weight balance (Table 3). It is surprising that a relatively incomplete protein (globin) can contribute so effectively to the "protein pool" as it must obviously be supplemented by the amino acids inadequately represented in globin drawn from some reserve store to produce cell protein or plasma protein. The whole globin in some dogs is more effectively used than the hemoglobin digests, suggesting that some of the globin may be used without much breakdown and loss of nitrogen.

In our first experiments with globin and hemoglobin we could not obtain absolutely convincing evidence that the globin was used to make plasma protein. In these early experiments the hemoglobin and globin were given intravenously and the pure

TABLE 3

Plasma and Laked Red Cells Intraperitoneally—Nitrogen Balance

Dog 43-141—Mongrel

Period No.	Blood proteins injected Total N	Total urinary N	Urea N + NH^s-N	Total undetermined urinary N	Circulating plasma protein level	A/G ratio Tiselius	R.B.C. hematocrit	Weight
48 hrs.	*gm.*	*gm.*	*per cent*	*gm.*	*gm. per cent*		*vol. per cent*	*kg.*
Basal diet contains little protein (0.86 gm. N per period)								
1		3.31	76.7	0.77	5.72		41	9.8
2		2.55	73.4	0.68				
3		2.08	68.7	0.55				
4		2.34						
Basal diet + whole blood plasma intraperitoneally								
5	4.60	1.80	75.5	0.44				9.4
6	4.17	2.53	83.5	0.42	7.64		38	
7	3.43	1.48	71.4	0.42				
8	1.86	1.30	65.8	0.45	8.90		45	9.3
9	3.80	1.61	67.4	0.52	9.70		40	
10	3.77	2.19	73.9	0.57				
11	2.07	2.70	69.9	0.82	9.98		41	9.4
12	3.81	2.52	72.3	0.70				
13	4.03	2.38	68.2	0.76				
14	4.06	2.14	69.3	0.66	9.32		35	9.5
Total	35.6	20.7						
Basal diet								
15		2.14	69.3	0.66		0.8	29	
16		2.00	63.7	0.73			30	
17		2.05	67.2	0.67	7.72		32	
18		1.69	66.0	0.57				
Basal diet + laked red blood cells intraperitoneally								
19	4.31	2.00	61.5	0.77	6.64	1.0	36	9.2
20	4.62	2.56	72.0	0.72	6.61		43	9.2
21	4.10	2.74	70.6	0.80	6.50		47	
22	1.80	2.40	66.7	0.80				
23	4.09	2.06	71.5	0.59				
24	4.30	3.39			6.93		51	
25	2.25	2.46						9.1
26	3.62	3.34					46	
27	3.80	1.86				0.5		
28	4.63	2.79						9.1
Total	37.5	25.6						
Basal diet								
29		2.88						
30		1.63						
31		1.60						9.0

(From Miller, L. L., Robscheit-Robbins, F. S., and Whipple, G. H.: *J. Exp. Med., 81:* 408, 1945.)

globin was toxic in large doses and the hemoglobin was lost through the kidney in considerable amounts. When the hemoglobin was given intraperitoneally there was a moderately prompt absorption but not sufficient to raise hemoglobin concentration in the plasma to the hemoglobinuria level. In such experiments (Tables 2 and 3) large amounts of hemoglobin could be given with results which are obvious. There are no untoward reactions and the contribution of hemoglobin to the "protein pool" is beyond doubt.

Utilization of Plasma Protein and Hemoglobin in Emergencies

Table 3 shows an uninterrupted period of 62 days which comes close to the perfect experiment. The dog was in perfect condition and ate the basal diet (very low protein intake) throughout. There is a slight gain in weight and a strong positive urinary nitrogen balance when dog plasma is given in large doses intraperitoneally. Utilization of plasma protein for body maintenance is obvious over a twenty-day period. Following a second control diet period, hemoglobin in large amounts was given intraperitoneally. There was only a very slight weight loss (0.1 kilo) in twenty days—the urinary nitrogen balance is positive but shows a slight increase (3.0 gm.) in output as compared with the plasma period. Evidently the globin is very well utilized to maintain the nitrogen balance of the body (11).

Pigment radicles derived from hemoglobin given intraperitoneally are thrown away and appear as surplus bile pigment, even when there is urgent need for all available nitrogenous material—given protein fasting, anemia, and hypoproteinemia in a bile fistula dog (Table 4). The body evidently prefers to *make* rather than conserve the pyrrol aggregate (pigment radicle).

Protein Digests Contribute to New Hemoglobin and Plasma Protein

Table 4 shows that under this regime the bile fistula dog loses weight more rapidly than the control dog (Table 3). The hemoglobin or globin is well utilized and the urinary nitrogen is close to balance. The large output of bile pigment as measured is about sixty per cent of the calculated bile pigment, using methods that

do not measure bile pigment in the urine up to 100 per cent of the calculated amounts. We know that the iron is carefully conserved but apparently the pigment radicle cannot be reutilized (11).

Hemoglobin (globin) *digests* contribute effectively to body maintenance of nitrogen equilibrium. These digests are about as

TABLE 4

Bile Pigment Excretion in Bile Fistula Dog Increased by Laked Red Cell Injections—Anemia and Hypoproteinemia

Dog 40-41—Bile fistula

Period No.	R.B.C. injected Total N	Total urinary N	Bile pigment excretion	Circulating plasma protein level	Hemoglobin	Weight
48 hrs.	*gm.*	*gm.*	*mg.*	*gm. per cent*	*gm. per cent*	*kg.*
Basal diet (0.86 gm. N per period)						
1		4.53	63	5.50	8.9	16.4
2		3.53	58			
3		2.73	68			
Basal diet+laked red blood cells intraperitoneally						
4	2.09	2.71	83			14.9
5	4.03	3.75	386		12.7	
6	2.54	4.97	525	5.50		
7	3.66	3.82	459			
8	2.26	3.30	222			14.1
9	4.63	3.07	391			
Total	19.2	21.6				
Basal diet						
10		3.51	192	4.83	15.4	13.6
11		3.19	104			
12		1.61	96			

(From Miller, L. L., Robscheit-Robbins, F. S., and Whipple, G. H.: *J. Exp. Med., 81:* 419, 1945).

effective as whole hemoglobin in maintaining nitrogen balance but cause a rise in undetermined nitrogen not seen when hemoglobin alone is given intraperitoneally (Table 5). Table 5 shows a satisfactory experiment with hemoglobin digest given intravenously. Hemoglobin digests may be toxic and there was slight intoxication

—urticaria and defecation in this experiment. This hemoglobin digest came from Eli Lilly and Company—a papain digest of beef red cells.

Given healthy dogs, fed abundant iron and protein-free or low

TABLE 5

Hemoglobin Digests Intravenously—Nitrogen Balance
Hemoglobin and Plasma Protein Levels

Dog 39-251

Period No.	Hemoglobin digests injected Total N	Total urinary N	Urea N + NH_3-N	Total undetermined urinary N	Circulating plasma protein level	R.B.C. hematocrit	Weight
48 hrs.	*gm.*	*gm.*	*per cent*	*gm.*	*gm. per cent*	*vol. per cent*	*kg.*
Basal diet (0.50 gm. N per period)							
1		1.48	59.5	0.60			
2		1.78	55.5	0.80	5.56	49	10.9
Basal diet + hemoglobin digest intravenously							
3	4.36	5.10	59.5	2.07			
4	4.36	3.55	60.3	1.41			10.8
5	4.36	5.33	66.8	1.77			
6	4.36	5.28	65.5	1.72			
7	4.36	4.08	70.5	1.20			
8	4.36	4.53	72.1	1.26			11.1
9	4.36	4.50	67.8	1.45	5.37	46	
Total	30.5	32.4		10.88			
Basal diet							
10		1.92	64.1	0.69			
11		1.76	60.4	0.70			11.0

(From Miller, L. L., Robscheit-Robbins, F. S., and Whipple, G. H.: *J. Exp. Med., 81:* 414, 1945.)

protein diets, with sustained depletion due to bleeding, we can study the capacity of these animals to produce simultaneously new hemoglobin and plasma protein. The reserve stores of blood protein producing materials in this way are largely depleted, and levels of six to eight gm. per cent for hemoglobin and four to

five gm. per cent for plasma protein can be maintained for considerable periods of time. Under such conditions, these *anemic and hypoproteinemic* dogs will use very efficiently a variety of *digests* (serum, hemoglobin, and casein) and the growth mixture

TABLE 6

Production of Hemoglobin and Plasma Protein Due to a Casein Digest

Period 1 wk.	Weight	Protein intake		Protein output				Production ratio plasma protein to hemoglobin	Ratio protein output to intake	Total nitrogen	
				Hemoglobin		Plasma protein					
		Type	Weekly	Level	Output per wk.	Level	Output per wk.			Intake	Urinary output
Dog No. 40-155. Casein digest P36092											
	kg.		*gm.*	*gm. per cent*	*gm.*	*gm. per cent*	*gm.*	*per cent*	*per cent*	*gm.*	*gm*
1	15.1	Digest—vein	182	5.1	41.1	6.6	20.0	51	—	—	25.1
2	14.8	Digest—vein	188	6.9	20.5	6.5	16.7	84	—	59.2*	25.2
3	14.0	Basal	26	6.8	10.0	6.0	8.2	85	—	—	14.7
4	13.3	Basal	30	5.9	10.7	5.9	7.4	72	25	8.8*	10.7
Total output net					62		45	73			
1	14.1	Digest—oral	144	6.3	27.5	5.0	17.8	67	—	—	—
2	13.7	Digest—oral	136	6.3	1.3	5.5	—	—	—	—	—
3	13.8	Digest—oral	131	7.7	13.9	5.3	8.1	61	—	—	—
4	13.5	Basal	18	6.2	22.5	4.8	12.2	57	25	—	—
Total output net					73		38	52			

* Combined figures for 2 periods.

(From Whipple, G. H., and Madden S. C.: *Medicine, 23: 222*, 1944.)

(Rose) of pure *amino acids*. Nitrogen balance is maintained and considerable new blood proteins are produced (14).

Anemia Plus Hypoproteinemia or Double Depletion

Table 6 shows two experiments in a doubly depleted dog (anemic and hypoproteinemic) with casein digests—one by vein and one by mouth. (There is a considerable interval between these two experiments). On the average, the digests are slightly

better utilized by mouth (14). There is a positive urinary nitrogen balance, slight weight loss, and good condition.

Amino acid mixtures are of especial interest. The growth mixture of ten amino acids (Rose) is well utilized by mouth, subcutaneously, intraperitoneally, or by vein and in the combination tested favors new hemoglobin production more than any test material. These ten essential amino acids are threonine, valine, leucine, isoleucine, lysine, tryptophane, phenylalanine, methionine, histidine and arginine. Glycine is usually added to this mixture (9). By mouth the amino acids are utilized a little more completely than when given parenterally. Our experiments give no evidence that the unnatural isomers of the amino acids are toxic and some are probably used in the body. These amino acid mixtures can be given rapidly in ten per cent solution parenterally and cause less clinical disturbance than any protein digests so far tested. Glutamic acid in digests or amino acid mixtures is not well tolerated by vein and may induce vomiting (8). Abundant production of plasma proteins in standardized dogs is readily demonstrated in experiments in which these amino acids are the sole source of nitrogen. The production of new hemoglobin and plasma protein due to amino acids in these experiments compares favorably with the response to high grade diet protein in equivalent amounts. Amino acids are well utilized in humans (1).

Amino Acids and Production of Hemoglobin and Plasma Protein

Table 7 shows two satisfactory experiments with the ten "essential" amino acids. Casein (dog 40-43) serves as a control. The ratio of protein output (hemoglobin and plasma protein) to protein intake (casein or amino acids) in these two experiments is about twenty per cent—a standard response. There is a satisfactory urinary nitrogen balance which is greater with casein than with amino acids. A large *reserve store* of hemoglobin and plasma protein is removed in dog 40-43, period 1. Period 7 (dog 40-43) shows a large blood protein output which obviously is a *carry over* from period 6—due to large intake of amino acids. Dog 40-32 (Table 7) shows the response to the ten growth amino acids by mouth and by vein. The output of hemoglobin is almost three

TABLE 7

Production of Hemoglobin and Plasma Protein Due to Amino Acids Necessary for Growth (Rose)

Period	Weight	Protein intake		Protein output				Total Nitrogen	
				Hemoglobin		Plasma protein		Intake	Urinary output
		Type	Weekly	Level	Output per wk.	Level	Output per wk.		
1 wk.	*kg.*		*gm.*	*gm. per cent*	*gm.*	*gm. per cent*	*gm.*	*gm.*	*gm.*
Dog 40-32. Amino acid mixture Ve daily									
1	13.9	Basal	34	6.8	1.7	4.7	0	—	—
2	13.8	Amino acid—oral	177	8.8	18.5	4.8	12.4	28.3	15.8
3	12.9	Amino acid—oral	177	7.5	38.0	4.9	19.8	28.3	15.8
4	12.8	Amino acid—vein	177	8.8	15.8	4.7	7.7	28.3	16.7
5	12.6	Basal	0	8.8	1.6	3.9	0	0	4.03
Total output net					89		34		
Dog 40-43. Amino acid mixture Vaa in varying dosage—subcutaneous. Casein as control by mouth. Basal diet in all periods.									
1	13.9	Basal	19	10.0	118.2	4.6	48.9		
2	13.3	Basal	19	9.3	19.4	4.6	6.8		
3	12.6	Casein	204	9.3	28.4	4.6	13.0		
4	13.2	Casein	204	7.6	38.7	4.9	17.7		
			Totals		67.1		30.7		
5	13.0	Amino acid×2	134	9.3	14.2	4.5	6.9	21.2	19.0
6	12.4	Amino acid×2	202	9.3	1.8	4.0	0	32.3	22.9
	0.8=6 per cent body weight loss		Totals		16.0		6.9	53.5	41.9
7	12.0	Amino acid ½ stand. dose	50	6.9	39.7	4.9	19.1	8	7.3
8	11.4	Amino acid ½ stand. dose	50	7.7	9.8	4.6	6.2	8	6.2
	1.0=8 per cent body weight loss		Totals		49.5		25.3	16	13.5
9	11.5	Amino acid stand. dose	100	7.4	25.2	4.7	12.0	16	8.9

(From Robscheit-Robbins, F. S., Miller, L. L., and Whipple, G. H.: *J. Exp. Med.*, *77*: 382, 1943.)

times as great as the plasma protein—89 to 34 gm. The urinary nitrogen comes up somewhat when amino acids are given by vein —a rise in the undetermined nitrogen, presumably amino acids.

Individual amino acids may or may not have a demonstrable influence upon body metabolism. As our knowledge grows in this

field it is probable that an increasing number of single amino acids can be shown to influence certain body processes.

Methionine and *threonine* when singly eliminated from the growth mixture of ten amino acids do effect a sharp rise in urinary

TABLE 8

Protein and Methionine Protect against Chloroform Poisoning

Dog No.	Low protein diet, weeks	Preliminary treatment	Duration of anaesthesia, min.	Fibrinogen		Clinical condition
				Before chloroform, mg. per 100 cc.	48 hrs. after chloroform, mg. per 100 cc.	
39–20	9	None	20	373	63*	Dead 40 hours
39-16	6	Lean beef	20	—	—	Normal
39-299	6	Lean beef	20	—	—	Normal
38-241	8	Plasma protein	20	—	352	Slight intox.
38-241	15	Plasma protein	20	370	205	Slight intox.
39-157	9	dl-methionine	40	450	421	Normal
39-157	13	None	15	327	38*	Dead 36 hours
39-12	6	dl-methionine	40	264	222	Normal
39-12	10	None	15	347	44	Dead 47 hours
39-164	4	dl-methionine	40	332	401	Normal
39-164	7	Amino acids†	20	368	50	Severe intox.
39-130	11	dl-methionine	40	478	419	Normal
39-130	14	Amino acids‡	20	375	165*	Dead 40 hours
39-10	7	None	10	387	130	Moderate intox.
39-10	10	dl-methionine	40	402	343	Slight intox.

* Twenty-four hours after chloroform.

† 1-tyrosine, 1-histidine, 1-alanine, 1-glutamic acid.

‡ 1-tryptophane, dl-phenylalanine, dl-isoleucine, 1-aspartic acid, 1-valine, dl-lysine.

(From Miller, L. L., Ross, J. F., and Whipple, G. H.: *Am. J. M. Sc., 200:* 741, 1940.)

nitrogen. This loss of nitrogen is corrected when the individual amino acid is replaced in the growth mixture (16).

Methionine Protects Against Liver Injury

Methionine (and to a lesser extent cystine) has a protective action against certain poisons. The anemic and hypoproteinemic dog is very susceptible to injury by chloroform anaesthesia. These dogs can scarcely tolerate 15 minutes chloroform anaesthesia and

twenty minutes is practically always fatal, due to extreme liver necrosis. Methionine (four-five gm.) given twenty to two hours before anaesthesia will prevent the liver damage and intoxication (Table 8). Methionine will also protect against Mapharsen liver injury (2).

Table 8 shows two groups of experiments in summary. The first group of five experiments gives evidence that meat protein by mouth or plasma protein by vein within 24 hours before chloroform anaesthesia will give more or less protection against the chloroform liver injury.

The second group of ten experiments shows that methionine has a remarkable protective action where given four to twenty-four hours before the chloroform anaesthesia. In fact these protein-depleted dogs given four to five gm. methionine will tolerate twice the lethal chloroform anaesthesia and give little or no evidence of liver injury and minimal or no clinical disturbance (12).

Raiding of Body Protein

Raiding of body protein to form blood protein can go to a fatal state when anemia and hypoproteinemia are maintained by bleeding while the dog is limited to a very low protein diet, plus fat, carbohydrate, iron, salts and vitamin accessories (basal diet). Evidently in this emergency the body attempts to correct the anemia and hypoproteinemia at the expense of the body tissues—its circulating proteins have a priority over the tissue and organ proteins (Table 9). In some dogs this *raiding may progress actively up to the terminal fatal state* but usually decreases in the final two or three weeks. As the body weight loss continues, individual organs and their component cells lose protein. This loss may be interpreted, in part at least, as a loss of enzymes or proenzymes. It is at least possible that the loss of cell enzymes may account for the diminished cell function (liver function decrease) and lessened blood protein production. There is no evidence of nitrogen waste due to tissue breakdown—rather that all nitrogen is conserved and used frugally. This is further evidence that the exchange between tissue protein and blood protein is in fact a part of the protein "ebb and flow" between cells and plasma, with no significant excess of protein breakdown and related nitrogen loss (20).

Table 9 is a good example of the raiding of body protein to form blood proteins which are removed by bleeding. Considerable *reserve* hemoglobin and plasma protein are removed in period 1. There is a steady weight loss. The production of needed hemoglobin and plasma protein continues at about fifty to sixty gm. weekly total through period 8. The production fails in the last three periods. Blood volume shrinkage is well known. At the end of

TABLE 9

Prolonged Blood Protein Depletion—Death

Raiding of body tissue protein to form blood proteins

Period	Weight	Protein intake		Food Cons.	Plasma vol.	Protein output			
						Hemoglobin		Plasma protein	
		Type	Weekly			Level	Output per wk.	Level	Output per wk.
1 wk.	*kg.*		*gm.*	*per cent*	*cc.*	*gm. per cent*	*gm.*	*gm. per cent*	*gm.*
1	21.8	Basal+squash	33	95	918	13.5	98.3	4.9	26.0
2	20.9	Basal+squash	29	82	928	11.8	52.3	4.4	17.9
3	20.0	Basal+salmon 75	28	81	816	11.0	37.5	4.6	11.7
4	19.3	Basal+salmon 75	120	87	966	11.0	35.8	4.5	12.0
5	—	Basal+salmon 75	114	91	—	8.0	33.5	5.2	15.4
6	17.6	Basal+salmon 40	83	80	992	8.0	39.6	5.0	23.4
7	16.8	Basal+squash	47	94	930	8.2	42.4	4.7	23.2
8	16.0	Basal+squash	38	80	886	6.5	33.0	4.2	17.2
9	15.2	Basal+squash	23	77	882	6.5	1.3	4.1	0
10	13.6	Basal+squash	17	79	774	7.3	19.9	4.2	10.5
11	12.9	Basal+squash	15	65	714	7.3	1.5	3.9	0
		Totals	547				395		157

8.9 kg. = 41 per cent body weight *loss*—3.7 per cent per wk.

(From G. H. Whipple, L. L. Miller, and F. S. Robscheit-Robbins: *J. Exp. Med., 85:* 278, 1947.)

period 11 the dog was placed on a liberal protein diet which was well eaten for four days. Dog was found dead—interstitial pneumonia, a terminal infection related to the great depletion of body proteins.

Maximal Hemoglobin Production

The *maximal output ceiling* for hemoglobin in anemia due to blood loss is about sixty gm. per week—the dog receiving a rich protein diet plus high iron intake. *Ferrous* and *ferric* salts are equally effective. Iron intravenously plus a rich protein diet may

push this level up to 90 to 100 gm. per week. Evidently iron absorption is a limiting factor in these experiments (Table 10).

Table 10 represents a large number of controlled experiments in *anemia due to blood loss* in otherwise healthy dogs. Apparently the dog under such conditions can use more iron than can be absorbed. Under ordinary conditions the dog would have a considerable reserve store of iron which would be drawn on in an emergency but these reserve stores of iron have been exhausted in these standard anemic dogs.

TABLE 10

Maximal Hemoglobin Production—Grams per Week
Standard Continuing Anemia of Six to Eight Gm. Hemoglobin

Dog No.	Dog average normal weight	Daily diet Liver 300 gm.	Daily diet Salmon bread plus iron 400–450 mg.			Daily diet Salmon bread, liver plus iron 400–450 mg.			Daily diet Liver, salmon bread plus iron by vein 24 mg.	
			Reduced	Ferric	Ferrous	Reduced	Ferric	Ferrous	Colloidal Fe	Estimated plasma protein removed
	kg.									
39-1	18.0	45*	60	51	50	62	58	66	92	71
40-26	14.5	50	59	45	60	56	63	—	80	49
37-21	18.0	41*	58	64	54	53	52	51	82	53
34-148	18.0	44*	49	49	54	47	63	71	106	58
34-145	20.0	47*	47	55	57	63	82	56	95	52
37-89	14.0	40*	32	54	42	39	48	47	84	47
33-14	12.0	38*	28	41	44	38	58	56	75	48
Average.....	16.3	44	48	51	52	51	61	58	88	54

* Average two to six experiments.

(From Robscheit-Robbins, F. S., Miller, L. L., and Whipple, G. H.: *J. Exp. Med., 82:* 314, 1945.)

The maximal output ceiling for hemoglobin and plasma protein in *doubly depleted dogs* (anemia and hypoproteinemia) may reach 120 to 130 gm. per week and using intravenous iron may reach 140 to 160 gm. per week (15).

Maximal output for plasma protein alone in *hypoproteinemia* due to plasmapheresis reaches sixty to seventy gm. per week but *this is not the true ceiling*. Technically we cannot remove the new plasma protein as fast as it is formed and the hypoproteinemia is not maintained in the face of a rich protein diet intake. Further-

more, the evidence points to the protein circulating pool contributing to the accretion of tissue protein in such dogs as well as doubly depleted dogs with a strong positive nitrogen balance and weight gain (Table 11).

TABLE 11

Maximal Blood Protein Production—Grams per Week
Anemia and Hypoproteinemia

Period 1 wk.	Weight	Protein intake		Protein output weekly					Ratio protein output to intake	Total nitrogen gm.	
				Hemoglobin		Plasma protein		Total output			
		Type	Weekly	Level	Output	Level	Output			Intake	Urinary output
	kg.		*gm.*	*gm. per cent*	*gm.*	*gm. per cent*	*gm.*	*gm.*	*per cent*	*gm.*	*gm.*
Dog 40-33											
1	18.5	Basal	19	8.6	26.3	3.9	9.0	35.3		3	9.3
2	18.6	Liver, beef, iron	973	7.8	89.0	5.1	44.9	133.9	14	157	37.4
3	18.8	" " "	1037	7.8	38.3	5.5	23.5	61.8	6	166	47.7
4	20.6	" " "	1037	9.5	69.4	5.4	38.6	108.0	10	166	57.0
5	20.2	" " "	1037	6.6	74.3	5.3	44.7	119.0	11	166	75.7
Average output per wk.					67.8		37.9	105.7			
6	20.7	Basal	19	6.6	23.3	4.6	10.7	34.0		3	18.3
7	18.3	"	19	10.3	17.9	3.8	6.6	24.5		3	10.1
Dog 37-85											
1	15.2	Basal	85	6.9	12.3	4.9	8.0	20.3		13	8.4
2	16.4	Liver, beef, iron	764	11.8	47.8	5.3	26.7	74.5	10	123	37.6
3	17.4	" " "	764	12.3	57.1	5.5	25.3	82.4	11	123	50.8
4	17.5	" " "	764	12.8	78.5	5.6	42.9	121.4	16	123	68.1
Average output per wk.					61.1		31.6	92.8			

(From Robscheit-Robbins, F. S., Miller, L. L., and Whipple, G. H.: *J. Exp. Med., 82:* 313, 1945.)

Maximal figures for *hemoglobin production* in anemia run close to one gm. hemoglobin per kilo per day. Maximal figures for *new hemoglobin plus plasma protein* production in simultaneous anemia and hypoproteinemia using iron given intravenously, may reach 1.5 gm. blood protein per kilo per day. The actual maximal *plasma protein production* equals about one gm. per kilo per day

but the true production ceiling cannot be reached by the plasmapheresis technique.

Infection Lessens Blood Protein Production

In contrast to the maximal figures recorded in Tables 10 and 11, we may refer to observations to show that *infection will lessen the*

TABLE 12

Infection—Endometritis

Dog 27-240. Bull, female, adult

Diet periods 1 wk. each	Food consumed	Weight	Plasma volume	R.B.C.	Blood hemoglobin level	Hemoglobin removed per week
Food, gm. per day	*per cent*	*kg.*	*cc.*	*mil.*	*per cent*	*gm.*
Bread 275, salmon 125, Klim 20	89	13.3	884	4.5	43	12.1
Bread 275, salmon 150, Klim 20	91	13.5	780	4.2	47	2.2
Bread 275, salmon 150, Klim 20	79	12.9	820	5.6	52	20.5
Bread 225, salmon 200, Klim 20	85	13.5	806	4.1	44	1.2
Pig kidney 300, bread 225	71	12.3	742	3.9	47	1.4
Pig kidney 300, bread 225	93	12.6	826	4.5	52	11.2
Bread 225, salmon 200, Klim 20	82	12.6	800	3.8	49	1.3
Bread 225, salmon 200, Klim 20	95	12.2	763	3.7	46	1.8
Bread 200, salmon 200, Klim 20	96	12.0	713	4.2	47	1.5
Hysterectomy—Transfusions (42 gm. hemoglobin)						
Bread 250, salmon 200, Klim 20	100	11.7	699	4.2	55	2.0
Bread 300, salmon 200, Klim 20	100	12.0	713	5.4	60	40.5
Bread 300, salmon 200, Klim 20	100	12.0	683	4.9	58	27.5
Bread 300, salmon 200, Klim 20	100	12.2	718	4.5	56	12.5
Bread 350, salmon 125, Klim 20	100	12.7	755	4.8	68	22.9
Bread 350, salmon 125, Klim 20	100	12.7	779	5.5	62	46.6
Bread 350, salmon 125, Klim 20	100	13.1	780	4.8	55	34.0
Bread 350, salmon 125, Klim 20	100	13.0	800	4.6	43	23.7
Bread 350, salmon 125, Klim 20	98	13.2	800	4.6	51	14.0
Bread 375, salmon 100, Klim 20	100	13.2	822		55	26.4
Bread 375, salmon 100, Klim 20	100	13.3	760	5.5	54	34.3

(From Robscheit-Robbins, F. S., and Whipple, G. H.: *J. Exp. Med., 63:* 773, 1936.)

production of hemoglobin or plasma protein and may in fact bring the production curve close to zero. For example (17), a standard anemic dog which developed an extensive endometritis showed a curve of hemoglobin production falling close to zero. Following operative removal of the infected uterus, the production curve rose

to, and even above, its normal level. Likewise, in a hypoproteinemia (plasmapheresis) given a series of sterile abscesses, there was a sharp fall in the output or production of plasma protein (7).

Table 12 shows a convincing experiment in a standard anemic dog which developed endometritis (due to catheterization). Before operation the response to liver feeding was about ten per cent of normal. The high response to the salmon-bread diet after the operation suggests some absorption and storage of hemoglobin producing factors during the intoxication period before operation. Other related experiments are listed elsewhere (17).

Liver—The Master Organ in Protein Metabolism

The liver is the master organ for various protein metabolic activities—it stores proteins, it makes proteins (fibrinogen, prothrombin, and probably other globulins and albumins), and it aggregates amino acids and other nitrogenous materials coming from the gastrointestinal tract into proteins. Whether these newformed proteins may be liver proteins first and subsequently proteins for exchange and distribution (plasma proteins) is beside the point.

The normal liver having this key position in protein metabolism, observations made upon a liver which is somewhat abnormal will be of interest to students of physiology and pathology. The Eck fistula liver qualifies in this respect and as time and occasion permitted we have made observations on Eck fistula dogs, often maintained in an apparent state of health for as many as eight years. At times these dogs present unusual disturbances of protein metabolism and again are close to normal. They appear normal in all respects, activity, appetite, digestion, and weight, but occasionally they may show increased thirst, diuresis, a trace of jaundice or lack of appetite, and vague intoxication. The fact that these dogs have tolerated an Eck fistula for from one to eight years speaks for a general state of good health (21).

Eck Fistula Liver

The Eck fistula permits the portal blood to flow freely into the vena cava and excludes portal blood from the liver. The blood supply to this liver is arterial and probably but 25 to 35 per cent

of normal. The Eck fistula liver is somewhat smaller than normal but there is no significant fibrosis. The liver cells here and there show fat droplets but for the most part appear normal. This liver may produce less bile salt than the normal control (18).

When the Eck fistula liver is put under the strain of producing blood proteins in an emergency (stimulus of anemia and hypoproteinemia), it is not surprising that it shows a lessened func-

TABLE 13

Eck Fistula Dog—Anemic and Hypoproteinemic Capacity to Produce Blood Proteins Falls after First Four Periods

Period No.	Daily diet	Period duration	Protein intake average per week	Weight average	Blood levels average		Protein output average per week		Protein ratio total output to intake
					Hemoglobin	Plasma protein	Hemoglobin	Plasma protein	
	mg. and gm.	*wks.*	*gm.*	*kg.*	*gm. per cent*	*gm. per cent*	*gm.*	*gm.*	*per cent*
1	Liver 150, basal	7	226	17.5	8.9	4.8	46.5	23.4	31
2	Liver 150, basal	6	226	16.8	8.7	4.9	40.1	19.6	26
3	Liver 150, basal	4	226	16.3	8.2	4.6	44.0	21.2	29
4	Liver 150, basal	4	226	16.3	6.9	4.6	33.8	18.1	23
5	Salmon 200, basal	10	277	18.3	7.1	5.0	15.7	9.0	9
6	Kidney 225, basal	5	269	18.9	7.4	5.2	34.8	19.9	20
7	Salmon 200, basal	2	277	18.5	7.0	5.1	11.5	7.1	6
8	Liver 200, basal	6	292	18.3	7.2	5.4	26.2	17.9	15
9	Salmon 200, basal	6	275	18.5	6.9	5.0	25.8	14.4	15
10	Salmon 200, basal	16	290	20.0	8.6	4.9	35.2	16.4	18
11	Salmon 200, basal	1	168	16.7	9.2	4.6	1.0	0	1
12	Salmon 150, liver 150	1	361	15.1	8.7	5.8	17.9	12.1	8
13	Salmon 100, liver 100, meat 150	1	435	15.7	7.0	6.3	44.6	28.9	17
14	Salmon 150, liver 225, basal	2	564	16.6	7.4	6.5	18.8	11.3	5

(From Whipple, G. H., Robscheit-Robbins, F. S., and Hawkins, W. B.: *J. Exp. Med., 81:* 171, 1945.)

tional capacity as compared with the non-Eck control (Table 13). Is *is* surprising that so often this liver can approach the performance of the normal control. This may be attributed to the well-known reserve capacity of the liver.

The Eck fistula dog (Table 13) responds at times like a normal (non-Eck) dog to the stimulus of anemia and hypoproteinemia (double depletion). In periods 1 to 4 inclusive the basal low protein diet plus liver is well utilized to form hemoglobin and plasma protein (protein ratio total output to intake 23 to 31 per cent). The ratio of hemoglobin to plasma protein is about two to one.

Salmon is less well used in periods 5 and 7—protein ratios of nine and six per cent. Period 5 is of considerable interest as the intake of protein was ample over a ten-week period with some gain

TABLE 14

Anemic Eck Fistula Dogs
Hemoglobin Production in Long Continued Anemia—Grams per Week

Dog. No.		Table No.	Liver oral	Liver extract with Fe oral	Kidney oral	Iron mg. daily	
						40 oral	400 oral
34-146	Early	1	44-27	—	26	22-25	25-28
	Late		34-31	43-42	13	6-20	—
39-77	Early	3	38-26	36	13	10-27	—
	Late		28-33	43	—	20	25
35-5 acacia	Before	5	19-26	—	18-23	11-24	19-27
	After		24	—	—	20	26
26-124 chloroform	Early	6	42-47	—	—	21-26	—
	Late		39-28	—	—	24-15	—
26-124 chloroform	Early	7	32	—	—	22-13	—
	Late		16-22	—	13-18	18-19	33
30-61	Early	8	25	—	—	25-14	—
	Late		42-28	—	—	18-15	22
24-90	Early	9	28	—	33	7-15	23
	Late		24	25-12	—	10	—
Non-Eck control dog		—	50-40	60-40	30-40	30-25	55-40

(From Whipple, G. H., Robscheit-Robbins, F. S., and Hawkins, W. B.: *J. Exp. Med., 81:* 171, 1945.)

of weight. In spite of anemia (7.1 gm. per cent) and moderate hypoproteinemia (5.0 gm. per cent), the output of total blood proteins was only 24.7 gm. per week. This is about one-half the expected output in a control non-Eck dog. Periods 7, 11 and 14 show still lower output levels.

One comes to recognize the response of the Eck fistula animal as decidedly variable month by month. The general tendency (Table 14) is for a *decrease in hemoglobin production* due to liver

feeding—higher in the periods following the Eck fistula operation and lowest as the history approaches the end. The response to iron feeding in small doses is low, but with larger doses of iron we note uniformly even lower output figures for hemoglobin production as compared to anemic non-Eck controls.

The experiments above indicate that the liver is concerned directly or indirectly with the production of new hemoglobin. Our belief is that the liver contributes to the fabrication of hemoglobin by means of the mobile plasma proteins which to a large extent derive from the liver.

Plasma Proteins Can Supply All Body Protein Needs

Plasma protein given as plasma parenterally *can supply all the protein needs of the body* over considerable periods of time. Provided the dog is given by mouth adequate amounts of carbohydrate, fat, salts and vitamin accessories, the dog will remain in health, weight, and nitrogen balance. Table 3 above shows a good experiment of twenty days. Other experiments to be published have extended this time beyond ninety days with similar results. The fact that in such experiments the albumin/globulin ratio is not significantly changed means that all the plasma proteins can be used in the body metabolism as the whole plasma is given day by day; otherwise, some one albumin or globulin would accumulate in the circulating plasma. No significant *hyperproteinemia* develops and there is no leakage and escape by way of the kidney. It seems proper to think of plasma proteins as ideally suited for *mobile exchange* within the total body protein pool (20).

Table 15 shows clearly that *dog plasma* can supply protein materials out of which the depleted dog can manufacture *new hemoglobin* in considerable quantities. When one gives dog plasma by vein to a depleted dog it would not be surprising if the subsequent continued daily bleedings removed most of the introduced plasma protein. On the contrary, the new hemoglobin is produced promptly and in large amounts—even in excess of the removed plasma protein.

Table 15 shows a total production of 125 gm. hemoglobin during periods 2 to 5 with no significant hyperproteinemia. These amounts are far too large to be attributed to hypothetical reserve

stores in depleted dogs and there is only slight weight loss. The beef serum digest is used as effectively as any digest (thirty per cent return from the injected protein digest) and there is considerable loss of weight. The ratio of new hemoglobin produced to

TABLE 15

Production of Hemoglobin and Plasma Protein Due to Dog Plasma and Beef Serum Digest

Period 1 week	Weight	Protein intake		Protein output				Production ratio plasma protein to hemoglobin
		Type	Weekly	Hemoglobin		Plasma protein		
				Level	Output per wk.	Level	Output per wk.	
Dog. No. 37-23. Whole fresh dog plasma by vein—60% return								
	kg.		*gm.*	*gm. %*	*gm.*	*gm. %*	*gm.*	*%*
1	16.8	Basal	76	10.1	12.4	4.1	5.4	
2	16.3	Dog plasma	154	8.3	50.0	7.1	33.4	67
3	16.5	Dog plasma	164	7.8	41.1	6.8	31.9	78
4	16.2	Basal	38	7.6	30.5	5.7	22.8	75
5	16.0	Basal	38	7.4	22.6	4.8	15.1	67
Total output net					125		109	87
Dog No. 37-23. Beef serum digest KB 2-47 by vein—30% return								
1	16.1	Serum digest	74	7.5	1.6	4.8	0	
2	15.4	Serum digest	117	7.7	45.2	5.1	22.1	51
3	15.5	Serum digest	117	7.7	1.6	4.8	0	
4	14.5	Basal	19	8.8	17.0	4.5	7.2	42
5	14.0	Basal	19	8.8	1.6	4.6	0	
Total output net					77		27	35

(From Whipple, G. H., and Madden, S. C.: *Medicine, 23:* 215, 1944.,

plasma protein produced is about three to one, indicating that this digest, theoretically perfectly suited to produce plasma proteins, does nevertheless favor hemoglobin production. There seems to be no reasonable doubt that *plasma proteins contribute freely to the formation of globin and hemoglobin.*

Evidence cited above indicates that protein molecules can *emerge* from a cell and also *enter* a cell readily—a dynamic equilibrium between cell and plasma protein. This forces us to consider how these large protein molecules pass in and out through cell surface membranes.

Surface membranes as described by Krogh (5) are ill-defined and closely bound up with the cell protoplasm of which they form the boundary zone. Such membranes restrict the free movement of molecules and particles but are not concerned with any energy requiring *transport* of substances across its thickness.

Surface membranes are generally believed to be a mixture of lipids, proteins and perhaps other substances. They may be arranged as a mosaic in which the proteins and other substances are distributed in a regular or haphazard manner (Rideal (13)). The arrangement may be in layers of protein and lipid material, giving a lipid-protein surface to the plasma membrane designated in its simplest form as a bimolecular layer of lipoid molecules between two layers of protein molecules (Harvey and Danielli (3)).

Physiologists have much to say about the behavior of electrolytes and small molecules as related to surface membrane passage but, in general, maintain a discreet silence about membrane passage of protein molecules. Perhaps this is evidence of wisdom, but our interest in the ebb and flow of proteins between the cell and blood plasma has forced us to speculate about it. If the surface membrane of the liver cells is a mixture of protein and lipid, these proteins must be intimately related to other cell proteins *including enzymes*. We can see no reason why these enzymes may not be able to modify the surface membrane so that cell proteins needed by the body can emerge as they are formed rapidly within the cell. Incoming proteins from the plasma protein pool could pass through the surface membrane in the same fashion, preceded by adsorption on the surface, when protein is needed within the cell.

The argument that these proteins are broken down to amino acids to permit surface membrane passage does not stand analysis —the *outgoing* protein if broken down at the surface would appear as amino acids in the blood plasma and be treated as such, there being no evidence that proteins are synthesized outside of the cell proper. If the incoming proteins were broken down to amino acids at the surface, we would expect some escape of the amino acids into the blood plasma and this reaction would be detectable in careful study of nitrogen metabolism (4). When a dog is kept in nitrogen and weight equilibrium for weeks by feeding sugar and fat by mouth and given plasma by vein, there is

evidence (4) that this plasma protein is used *without wastage* of nitrogen, in contrast to the findings when protein is fed. We have assumed from this and other evidence that the introduced plasma protein passed into body cells needing protein and within the cell was modified by enzyme activity to furnish the particular protein needed (liver, muscle and others).

Stimuli Affecting Blood Proteins

Stimuli which are responsible for the *increase* in any given *blood protein* should be mentioned, even if little can be said other than that our ignorance is almost complete. It is believed that anoxemia is a stimulus to hemoglobin production but it is probable that other factors enter the reaction. The stimuli responsible for plasma protein production certainly are variable. Who will even guess at the nature of the stimulus relating to the production of fibrinogen by the liver? Fibrinogen is a labile protein which may show wide fluctuations within the space of a day or so, related to liver injury, tissue injury, hemorrhage, and many other factors (6). Fibrinogen normally makes up but ten per cent of the plasma globulins, so that one cannot say that any significant change in osmotic pressure is responsible for or related to these changes in fibrinogen. We may say a nice balance between use and production of fibrinogen is maintained at about 0.3 gm. per 100 cc. in the plasma of the normal dog, but the stimuli which change this level are various and their mode of operation quite obscure. It is probable that hypoproteinemia in some obscure manner does accelerate the production of new plasma albumin and globulin but the fact that proteins can pass to and fro easily between cells and plasma makes the interpretation of experiments difficult.

Figure 1 is an attempt to picture certain features of protein metabolism as we see it (19). We believe that the liver is strategically situated and of sufficient size to take on most of the work of *protein synthesis*. Many plasma proteins emerge from the liver cells and can be used in the body to supply all or most of its protein requirements. Figure 1 indicates by arrows that the liver cell can store protein and that it can give out stored protein or fabricated protein. The protein on its way out or in is simply designated as transition protein which by cleavage and reassembly (enzymes) is

on its way to cell protein or plasma protein. Much cell protein cannot be removed and is called indispensable. Parenchyma or tissue cells, including muscle cells, as indicated by arrows can act to store proteins or to use proteins or to release stores and perhaps to fabricate protein in a small way. We believe the plasma protein can contribute to the manufacture of red cell hemoglobin but there

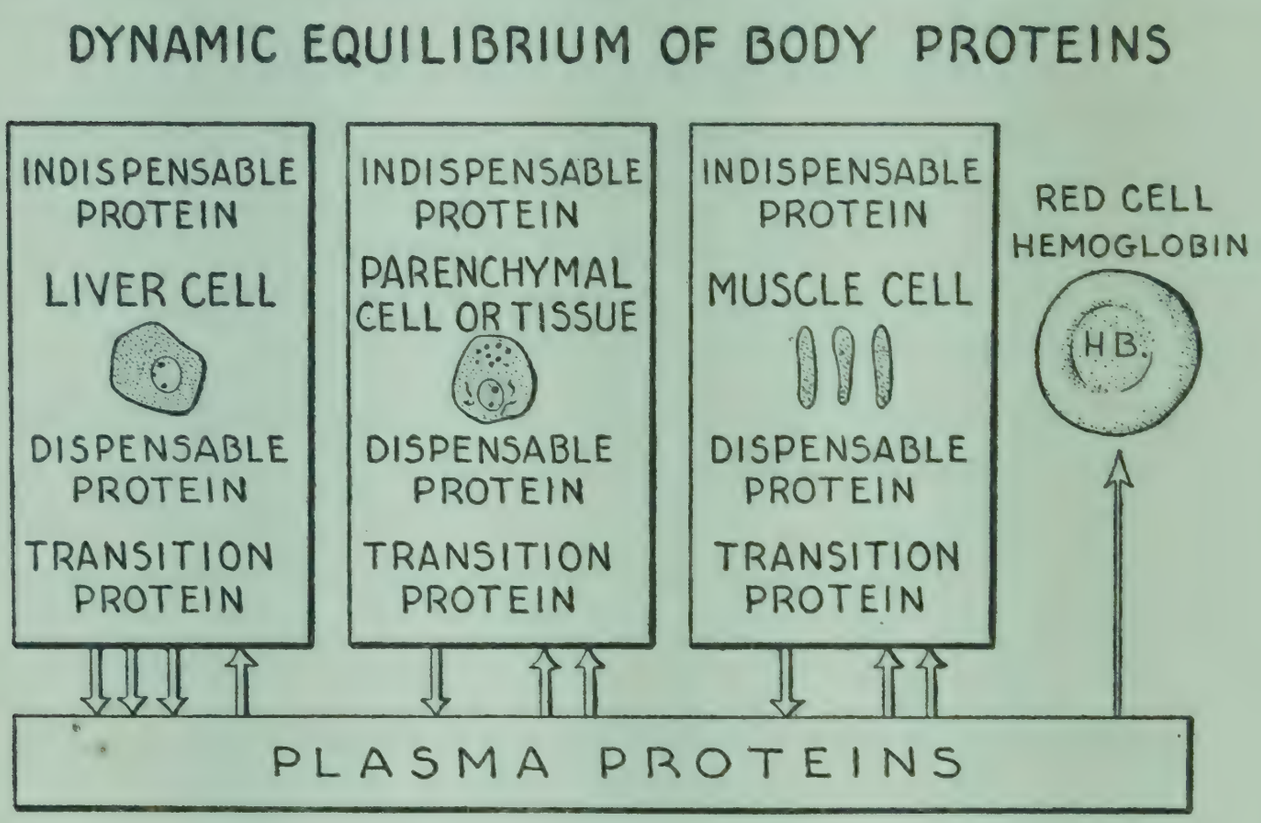

FIG. 1.

(From Whipple, G. H.: *Am. J. M. Sc., 203:* 11, 1942.)

is no evidence of an outflow of protein from these red cells short of cell breakdown.

Hemoglobin in its production may draw on the plasma protein but hemoglobin stands apart in the protein economy and does not contribute freely to the protein pool. On the other hand, the body guards jealously the fabrication of hemoglobin and given a real need for both plasma protein and hemoglobin (anemia and hypoproteinemia), the protein flow favors hemoglobin. Under these circumstances hemoglobin always is produced in more abundance than the plasma protein—usually two or three to one.

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Their Production and Interchange

By

G. H. WHIPPLE, M.D.

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